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* * * * * * * * * * * * * * STN  Columbus * * * * * * * * * * * * * *

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=> index biosci -uspatfull -uspat2
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                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.84       0.84

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      AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
      CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
      DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 12:40:09 ON 22 MAY 2006

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=> s urease (10a) chemotherap?
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          7   FILE CAPLUS
          6   FILE DGENE
          1   FILE DRUGU
          1   FILE EMBASE
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          1   FILE JICST-EPLUS
          5   FILE MEDLINE
          1   FILE PASCAL
          1   FILE SCISEARCH
          2   FILE TOXCENTER
          1   FILE VETU

  11 FILES HAVE ONE OR MORE ANSWERS,   66 FILES SEARCHED IN STNINDEX

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          0*  FILE AQUALINE
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          0*  FILE BIOTECHNO
          0*  FILE CEABA-VTB
          0*  FILE CIN
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          0*  FILE FOMAD
          0*  FILE FOREGE
          0*  FILE FROSTI
          0*  FILE FSTA
          0*  FILE KOSMET
          0*  FILE NTIS
          0*  FILE NUTRACEUT
          0*  FILE PASCAL
          0*  FILE PHARMAML
  56 FILES SEARCHED...
          0*  FILE WATER

   1 FILES HAVE ONE OR MORE ANSWERS,   66 FILES SEARCHED IN STNINDEX

L2    QUE L1 (P) TARGET?

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=> s l1
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          7   FILE CAPLUS
          6   FILE DGENE
          1   FILE DRUGU
          1   FILE EMBASE
  35 FILES SEARCHED...
          1   FILE JICST-EPLUS
          5   FILE MEDLINE
          1   FILE PASCAL
          1   FILE SCISEARCH
          2   FILE TOXCENTER
          1   FILE VETU

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L3    QUE L1

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L5 20 DUP REM L4 (7 DUPLICATES REMOVED)

=> s l5 and target?
L6 8 L5 AND TARGET?

=> d l6 bib ab 1-8

L6 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:985203 CAPLUS <<LOGINID::20060522>>
DN 143:260354
TI Method and composition using a weakly basic anticancer compound and urease for inhibiting cancer cell growth
IN Segal, Donald; McElroy, Jerry; Chao, Heman; Wong, Wah Y.; Docherty, John; Dickstein, Jodi
PA Helix Biopharma Corporation, Can.
SO U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 621,833.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 2005196391 | A1 | 20050908 | US 2005-46271 | 20050127 |
| | US 2004115186 | A1 | 20040617 | US 2003-621833 | 20030716 |
| PRAI | US 2002-397244P | P | 20020718 | | |
| | US 2003-621833 | A2 | 20030716 | | |

AB Improvements in methods of treating cancer with weakly basic anticancer compds. are provided. In one aspect, the invention provides an improvement in a method of treating cancer cells whose extracellular environment contains 1-8 mM urea, by exposing the cells to a weakly basic anticancer compd. which is effective in inhibiting the growth of the cells. The improvement includes (a) exposing the cells to a urease enzyme compn. and, (b) by step (a), reducing the amt. of anticancer compd. required to produce a given extent of inhibition in the growth of the cells when the cells are exposed to the anticancer agent. Methods of potentiating the specific therapeutic activity of a weakly basic anticancer compd. in the treatment of a given mammalian cancer which is responsive to the compd. are provided as are pharmaceutical compns. for use in i.v. administration to a subject are also provided.

L6 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1997:335117 CAPLUS <<LOGINID::20060522>>
DN 126:301778
TI ***Urease*** inhibitors as ***chemotherapeutic*** agents for mycobacteria
IN Horwitz, Marcus A.; Clemens, Daniel L.; Lee, Bai-Yu
PA The Regents of the University of California, USA; Horwitz, Marcus A.; Clemens, Daniel L.; Lee, Bai-Yu
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9712057 | A1 | 19970403 | WO 1996-US15303 | 19960924 |
| | W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN | | | | |
| | AU 9671657 | A1 | 19970417 | AU 1996-71657 | 19960924 |
| PRAI | US 1995-4270P | P | 19950925 | | |
| | WO 1996-US15303 | W | 19960924 | | |

AB A method is claimed for treating mammals which are infected with a mycobacterium wherein the mycobacterium produces a urease. The method involves treating the mammal with an anti-urease agent to reduce the prodn. of urease by the mycobacterium and thereby reduce biol. activity of the mycobacterium. Anti-urease agents include urease inhibitors and oligodeoxynucleotides anti-sense to the urease gene or mRNA derived therefrom which prevents expression by the mycobacterium. Methods for screening compds. for potential use as anti-mycobacterium agents are also disclosed as in the identity of urease produced by M. tuberculosis. The urease provides a ***target*** to which anti-bacterial agents can be directed.

L6 ANSWER 3 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN
AN AAW14495 Protein DGENE
TI Treating mammals infected with Mycobacteria - by inhibiting proliferation of mycobacteria using urease inhibitor
IN Clemens D L; Horwitz M A; Lee B
PA (REGC) UNIV CALIFORNIA.
PI WO 9712057 A1 19970403 53
AI WO 1996-US15303 19960924
PRAI US 1995-4270 19950925

DT Patent
LA English
OS 1997-212916 [19]
CR N-PSDB: AAT63512
DESC Urease accessory molecule F.
AB Urease subunits A, B and C (AAW14492-94) and urease accessory molecules F and G (AAW14495-96) are respectively encoded by DNA sequences (AAT63509-13) from the urease gene cluster (AAT63514) of Mycobacterium tuberculosis strain Erdman. The urease (see also AAW14497) is important to pathogenesis and is therefore a suitable ***target*** for the design of anti-mycobacterial agents. Methods are provided for reducing proliferation of mycobacteria by exposure to anti- ***urease*** agents (e.g. antisense oligonucleotide and ***chemotherapeutics*** ) and for screening potential anti-mycobacterial agents utilising cell cultures infected with urease-producing mycobacteria.

L6 ANSWER 4 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN
AN AAW14494 Protein DGENE
TI Treating mammals infected with Mycobacteria - by inhibiting proliferation of mycobacteria using urease inhibitor
IN Clemens D L; Horwitz M A; Lee B
PA (REGC) UNIV CALIFORNIA.
PI WO 9712057 A1 19970403 53
AI WO 1996-US15303 19960924
PRAI US 1995-4270 19950925
DT Patent
LA English
OS 1997-212916 [19]
CR N-PSDB: AAT63511
DESC Urease subunit C.
AB Urease subunits A, B and C (AAW14492-94) and urease accessory molecules F and G (AAW14495-96) are respectively encoded by DNA sequences (AAT63509-13) from the urease gene cluster (AAT63514) of Mycobacterium tuberculosis strain Erdman. The urease (see also AAW14497) is important to pathogenesis and is therefore a suitable ***target*** for the design of anti-mycobacterial agents. Methods are provided for reducing proliferation of mycobacteria by exposure to anti- ***urease*** agents (e.g. antisense oligonucleotide and ***chemotherapeutics*** ) and for screening potential anti-mycobacterial agents utilising cell cultures infected with urease-producing mycobacteria.

L6 ANSWER 5 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN
AN AAW14493 Protein DGENE
TI Treating mammals infected with Mycobacteria - by inhibiting proliferation of mycobacteria using urease inhibitor
IN Clemens D L; Horwitz M A; Lee B
PA (REGC) UNIV CALIFORNIA.
PI WO 9712057 A1 19970403 53
AI WO 1996-US15303 19960924
PRAI US 1995-4270 19950925
DT Patent
LA English
OS 1997-212916 [19]
CR N-PSDB: AAT63510
DESC Urease subunit B.
AB Urease subunits A, B and C (AAW14492-94) and urease accessory molecules F and G (AAW14495-96) are respectively encoded by DNA sequences (AAT63509-13) from the urease gene cluster (AAT63514) of Mycobacterium tuberculosis strain Erdman. The urease (see also AAW14497) is important to pathogenesis and is therefore a suitable ***target*** for the design of anti-mycobacterial agents. Methods are provided for reducing proliferation of mycobacteria by exposure to anti- ***urease*** agents (e.g. antisense oligonucleotide and ***chemotherapeutics*** ) and for screening potential anti-mycobacterial agents utilising cell cultures infected with urease-producing mycobacteria.

L6 ANSWER 6 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN
AN AAW14492 Protein DGENE
TI Treating mammals infected with Mycobacteria - by inhibiting proliferation of mycobacteria using urease inhibitor
IN Clemens D L; Horwitz M A; Lee B
PA (REGC) UNIV CALIFORNIA.
PI WO 9712057 A1 19970403 53
AI WO 1996-US15303 19960924
PRAI US 1995-4270 19950925
DT Patent
LA English
OS 1997-212916 [19]
CR N-PSDB: AAT63509
DESC Urease subunit A.
AB Urease subunits A, B and C (AAW14492-94) and urease accessory molecules F and G (AAW14495-96) are respectively encoded by DNA sequences (AAT63509-13) from the urease gene cluster (AAT63514) of Mycobacterium tuberculosis strain Erdman. The urease (see also AAW14497) is important to pathogenesis and is therefore a suitable ***target*** for the design of anti-mycobacterial agents. Methods are provided for reducing proliferation of mycobacteria by exposure to anti- ***urease*** agents (e.g. antisense oligonucleotide and ***chemotherapeutics*** ) and for screening potential anti-mycobacterial agents utilising cell cultures infected with urease-producing mycobacteria.

L6 ANSWER 7 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN
AN AAW14497 Protein DGENE
TI Treating mammals infected with Mycobacteria - by inhibiting proliferation of mycobacteria using urease inhibitor
IN Clemens D L; Horwitz M A; Lee B
PA (REGC) UNIV CALIFORNIA.
PI WO 9712057 A1 19970403 53
AI WO 1996-US15303 19960924
PRAI US 1995-4270 19950925
DT Patent
LA English
OS 1997-212916 [19]
CR N-PSDB: AAT63514
DESC Urease protein.
AB The urease (AAW14497) of Mycobacterium tuberculosis strain Erdman comprises urease subunits A, B and C (see also AAW14492-94) and urease accessory molecules F and G (see also AAW14495-96) and is encoded by a urease gene complex (AAT63514). The urease is important to pathogenesis and is therefore a suitable ***target*** for the design of anti-mycobacterial agents. Methods are provided for reducing proliferation of mycobacteria by exposure to anti- ***urease*** agents (e.g. antisense oligonucleotide and ***chemotherapeutics*** ) and for screening potential anti-mycobacterial agents utilising cell cultures

infected with urease-producing mycobacteria.

L6 ANSWER 8 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN
AN AAW14496 Protein DGENE
TI Treating mammals infected with Mycobacteria - by inhibiting proliferation of mycobacteria using urease inhibitor
IN Clemens D L; Horwitz M A; Lee B
PA (REGC) UNIV CALIFORNIA.
PI WO 9712057 A1 19970403 53
AI WO 1996-US15303 19960924
PRAI US 1995-4270 19950925
DT Patent
LA English
OS 1997-212916 [19]
CR N-PSDB: AAT63513
DESC Urease accessory molecule G.
AB Urease subunits A, B and C (AAW14492-94) and urease accessory molecules F and G (AAW14495-96) are respectively encoded by DNA sequences (AAT63509-13) from the urease gene cluster (AAT63514) of Mycobacterium tuberculosis strain Erdman. The urease (see also AAW14497) is important to pathogenesis and is therefore a suitable ***target*** for the design of anti-mycobacterial agents. Methods are provided for reducing proliferation of mycobacteria by exposure to anti- ***urease*** agents (e.g. antisense oligonucleotide and ***chemotherapeutics*** ) and for screening potential anti-mycobacterial agents utilising cell cultures infected with urease-producing mycobacteria.

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FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 55.78 | 59.06 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
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| CA SUBSCRIBER PRICE | -1.50 | -1.50 |

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=> index biosci -uspatfull -uspat2 -dgene
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
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| FULL ESTIMATED COST | 0.61 | 59.67 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
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| CA SUBSCRIBER PRICE | 0.00 | -1.50 |

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65 FILES IN THE FILE LIST IN STNINDEX

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=> s (chemotherap? (10a) target?) and urease
1 FILE CAPLUS
30 FILES SEARCHED...

1 FILES HAVE ONE OR MORE ANSWERS, 65 FILES SEARCHED IN STNINDEX

L7 QUE (CHEMOTHERAP? (10A) TARGET?) AND UREASE

=> s (targeting (w) moiety) and urease
1 FILE BIOTECHABS
1 FILE BIOTECHDS
1 FILE CAPLUS
30 FILES SEARCHED...
3 FILE IFIPAT
2 FILE WPIDS
2 FILE WPINDEX

6 FILES HAVE ONE OR MORE ANSWERS, 65 FILES SEARCHED IN STNINDEX

L8 QUE (TARGETING (W) MOIETY) AND UREASE

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
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| FULL ESTIMATED COST | 1.83 | 61.50 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | 0.00 | -1.50 |

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FILE 'BIOTECHABS' ACCESS NOT AUTHORIZED

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L9 264 L8]

=> s l8
L10 7 L8

=> s l10 not l6
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THE L# REFERENCING L5 CANNOT BE USED. PLEASE CONTACT AN STN HELP DESK.
THE L# REFERENCING L5 CANNOT BE USED. PLEASE CONTACT AN STN HELP DESK.
L11 0 L10 NOT L6

=> d l10 bib ab 1-7

L10 ANSWER 1 OF 7 IFIPAT COPYRIGHT 2006 IFI on STN
AN 10957658 IFIPAT;IFIUDB;IFICDB <<LOGINID::20060522>>
TI METHOD AND COMPOSITION FOR INHIBITING CANCER CELL GROWTH
INF Chao; Heman, Aurora, CA
Dickstein; Jodi, Markham, CA
Docherty; John, Richmond Hill, CA
McElroy; Jerry, Richmond Hill, CA
Segal; Donald, Stouffville, CA
Wong; Wah Y., Edmonton, CAM
IN Chao Heman (CA); Dickstein Jodi (CA); Docherty John (CA); McElroy Jerry (CA); Segal Donald (CA); Wong Wah Y (CA)
PAF Helix BioPharma Corporation
PA Helix BioPharma Corp
AG PERKINS COIE LLP, P.O. BOX 2168, MENLO PARK, CA, 94026, US
PI US 2005196391 A1 20050908
AI US 2005-46271 20050127
RLI US 2003-621833 20030716 CONTINUATION-IN-PART PENDING
PRAI US 2002-397244P 20020718 (Provisional)
FI US 2005196391 20050908
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
PARN This application is a continuation-in-part of U.S. patent application Ser. No. 10,621,833, filed Jul. 16, 2003, U.S. Publication No. 2004/0115186 A1, published Jun. 17, 2004, which claims priority to and benefit of U.S. Provisional Patent Application No. 60/397,244, filed Jul. 18, 2002. Both of these applications are incorporated herein by reference in their entirety for all purposes.
CLMN 22
GI 13 Figure(s).
FIGS. 1A-1D illustrate the steps of the ***urease*** reaction. Urea is cleaved by ***urease*** to produce one molecule of ammonia and one of carbamate (A). Carbamate spontaneously decomposes to ammonia and carbonic acid (B). The carbonic acid equilibrates in water (C), as do the two molecules of ammonia, which become protonated to yield ammonium and hydroxide ions (D). The reaction results in a rise in the pH of the reaction environment.
FIG. 2 shows the mass spectrometry profile of a crude sample containing ***urease*** prepared in accordance with one embodiment of the invention.
FIG. 3 illustrates the affinity purification profiles of ***urease*** during various stages of the purification process, in accordance with another embodiment of the invention.
FIG. 4 illustrates the purification of E-coil-alpha hEGFR IgG conjugate by a protein-G column prepared according to one embodiment of the invention.
FIG. 5 shows the antibody titer of purified E-coil-alpha hEGFR IgG conjugate prepared according to one embodiment of the invention as determined by immobilized K-coil ELISA.
FIG. 6A is a graph showing a dose-response curve of urea on the viability of A549 (upward-trinagle-filled) and MDA-MB-231 ( small-circle) cells. Cells were incubated in 0-40 mM urea, treated with 2 U/ml of ***urease*** and incubated at 37 degrees C. for 2 hours as more fully described in Example 7. Viability of the treated cells began to drop as the urea level increased. Urea alone has no effects on A549 (Delta) and MDA-MB-231 (. xcirc.) controls.
FIG. 6B is a graph showing a dose-response curve of ***urease*** on the viability of A549 (upward-trinagle-filled) and MDA-MB-231 (small-circle) cells. Cells were incubated in 20 mM urea and treated with 2 U/ml of ***urease*** for 2 hours as described in Example 7. A549 (upward-trinagle-filled) were more susceptible to ***urease*** than MDA-MB-231 (small-circle) cells.
FIG. 6C is a graph showing total ammonium ion as a function of urea treatment in pooled incubation buffer collected from A549 cells treated with ***urease*** as described for FIG. 6A and as more fully described in Example 8. Hydrolysis of urea by ***urease*** (*) caused an increase in ammonium content as compared to the control (.squ.). Values are means+-S.D. of 4 replicates from 3 experiments.
FIG. 6D is a graph of pH as a function of urea treatment in pooled incubation buffer collected from A549 cells treated with ***urease*** as described for FIG. 6A and as more fully described in Example 8. Hydrolysis of urea by ***urease*** (*) caused an increase in pH as compared to the control (.squ.). Values are means+-S. D. of 4 replicates from 3 experiments.
FIGS. 7A-7F are graphs depicting the protective effects of acetohydroxamic acid (AHA) on ***urease*** cytotoxicity as described in Example 9. (A) A549 cells (upward-trinagle-filled) and (B) MDA-MB-231 cells (small-circle) treated with 2 U/ml of ***urease*** were protected from the cytotoxic effects by addition of acetohydroxamic acid to the incubation buffer. AHA alone at concentrations up to 6 mM was not toxic to both cell lines (no ***urease*** controls: Delta, A549; .xcirc., MDA-MB-231). Complete protection was observed at dose >== 2 mM. (C) AHA inhibited ammonium production by ***urease*** (*), which corresponds to an increase in survival rate of both cell lines as shown in (A) and (B). Higher amount of AHA (6 mM) can reduce the ammonium level close to that of control (.squ.). Values are means+-S.D. of 4 replicates from 3 experiments. (D) AHA inhibited ammonium production by ***urease*** at indicated urea concentrations; (E) A549 cells; or MDA-MB-231 cells incubated in the indicated amounts of urea and treated with 2 U/ml ***urease*** were protected from the cytotoxic effects of ***urease*** by addition of acetohydroxamic acid to the incubation buffer.
FIGS. 8A-8B are graphs which depict the growth inhibitor effects of ***urease*** on tumor cell line xenografts as described in Example 10. (A) ***urease*** inhibits the growth of established MCF-7 xenografts. The breast tumor stopped to grow after the second injection of high-dose of ***urease*** (10 U/injection, solid bars) on day 9 as compared to the controls (open bars). Time of intratumoral injections are indicated

by Delta below the x-axis. (B) effects of multiple low-dose (1 U/injection, hatched bars) and medium-dose (4 U/injection, solid bars) injections of ***urease*** on established A549 xenografts. Intratumoral injections were performed on days 5, 7, 9, 11 and 13 (Delta). Delay of tumor growth was observed from days 17 onwards as compared to the controls (open bars). Significance was determined using the two-tailed unpaired Student's t test: *P<0.05 and **P<0.005.

FIGS. 9A-9B are graphs depicting the effects of ***urease*** on the cytotoxicity of weakly basic anticancer drugs as described in Example 11. (A) lung tumor A549 and (B) breast tumor MDA-MB-231 incubated in 0, 2 or 8 mM urea, were treated with 2 U/ml of ***urease*** , and either 50 mu M of doxorubicin or 100 mu M of vinblastine at pH 6.8 overnight. The antitumor efficacies of the two compounds were enhanced at the presence of ***urease*** (solid bars) and urea as compared to the control (open bars). The solid circle (small-circle) indicates the pH of ureasetreated group measured after treatment. Values are means+-S.D. of 4 replicates from 3 experiments.

FIGS. 10A-10B are graphs showing the effects of ***urease*** on the cytotoxicity of weakly basic anticancer drugs as described in Example 11. Lung tumor A549 (A) and breast tumor MDA-MB-231 (B) were incubated in urea and treated with DOS47 (2 U/ml), and either Fluorouracil (13.3 mM) or Mitoxantrone (5 mu M) at pH 6. 8 overnight. The enhanced anticancer effect (solid bar) of Mitoxantrone is only observed in MDA-MB-231 but not in A549 cells. DOS47 also enhances the anticancer effects of Fluorouracil in A549 but not in MDA-MB-231. The solid circle ( small-circle) denotes the pH of DOS47 group measured after treatment. Values are means+-S.D. of 4 replicates from 3 different experiments.

OF 7 IFIPAT COPYRIGHT 2006 IFI on STN

AB Improvements in methods of treating cancer with weakly basic anti-cancer compounds are provided. In one aspect, the invention provides an improvement in a method of treating cancer cells whose extracellular environment contains 1-8 mM urea, by exposing the cells to a weakly basic anti-cancer compound which is effective in inhibiting the growth of the cells. The improvement includes (a) exposing the cells to a ***urease*** enzyme composition and, (b) by step (a), reducing the amount of anti-cancer compound required to produce a given extent of inhibition in the growth of the cells when the cells are exposed to the anti-cancer agent. Methods of potentiating the specific therapeutic activity of a weakly basic anti-cancer compound in the treatment of a given mammalian cancer which is responsive to the compound are provided as are pharmaceutical compositions for use in intravenous administration to a subject are also provided.

L10 ANSWER 2 OF 7 IFIPAT COPYRIGHT 2006 IFI on STN

AN 10607963 IFIPAT;IFIUDB;IFICDB <<LOGINID::20060522>>

TI METHOD AND COMPOSITION FOR INHIBITING CANCER CELL GROWTH; A ***UREASE*** ENZYME, AND HAVING ASSOCIATED WITH IT A CHEMICAL ENTITY EFFECTIVE TO ENHANCE THE DELIVERY OF THE ENZYME TO CANCER CELLS

INF Chao; Heman, Aurora, CA
Dickstein; Jodi, Markham, CA
Docherty; John, Aurora, CA
McElroy; Jerry, Richmond Hill, CA
Segal; Don, Stouffville, CA
Wong; Wah, Edmonton, CA

IN Chao Heman (CA); Dickstein Jodi (CA); Docherty John (CA); McElroy Jerry (CA); Segal Don (CA); Wong Wah (CA)

PAF Unassigned

PA Unassigned Or Assigned To Individual (68000)

PPA Helix BioPharma Corp CA (Probable)

AG PERKINS COIE LLP, P.O. BOX 2168, MENLO PARK, CA, 94026, US

PI US 2004115186 A1 20040617

AI US 2003-621833 20030716

PRAI US 2002-397244P 20020718 (Provisional)

FI US 2004115186 20040617

DT Utility; Patent Application - First Publication

FS CHEMICAL
APPLICATION

PARN This application claims priority to and benefit of U.S. Provisional Patent Application Serial No. 60/397,244, filed Jul. 18, 2002, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

CLMN 50

GI 5 Figure(s).

FIGS. 1A-1D illustrate the steps of the ***urease*** reaction. Urea is cleaved by ***urease*** to produce one molecule of ammonia and one of carbamate (A). Carbamate spontaneously decomposes to ammonia and carbonic acid (B). The carbonic acid equilibrates in water (C), as do the two molecules of ammonia, which become protonated to yield ammonium and hydroxide ions (D). The reaction results in a rise in the pH of the reaction environment;

FIG. 2 shows the mass spectrometry profile of a crude sample containing ***urease*** prepared in accordance with one embodiment of the invention;

FIG. 3 illustrates the affinity purification profiles of ***urease*** during various stages of the purification process, in accordance with another embodiment of the invention;

FIG. 4 illustrates the purification of E-coil-alpha hEGFR IgG conjugate by a protein-G column prepared according to one embodiment of the invention; and

FIG. 5 shows the antibody titer of purified E-coil-alpha hEGFR IgG conjugate prepared according to one embodiment of the invention as determined by immobilized K-coil ELISA.

OF 7 IFIPAT COPYRIGHT 2006 IFI on STN

AB A pharmaceutical composition and method for use in inhibiting growth of cancer cells in a mammalian subject are disclosed. The composition includes a ***urease*** enzyme, and associated therewith, a chemical entity effective to enhance the delivery of the enzyme to cancer cells, when the composition is administered to the subject. Also disclosed are a method of enhancing the effectiveness of weakly basic anti-tumor compounds, a method assessing the presence, size or condition a solid tumor in a subject, and a gene therapy composition for treating a cancer in a subject.

L10 ANSWER 3 OF 7 IFIPAT COPYRIGHT 2006 IFI on STN

AN 04165588 IFIPAT;IFIUDB;IFICDB <<LOGINID::20060522>>

TI METHODS FOR MEASURING IN VIVO CYTOKINE PRODUCTION; THROUGH IN VIVO CAPTURE BY LABELED BINDING REAGENTS FOLLOWED BY IN VITRO MEASUREMENT OF SERUM LEVELS; FOR MONITORING HUMAN/ANIMAL IMMUNOLOGICAL FUNCTION; SOLID PHASE SYNTHESIS

INF Finkelman; Fred D., Cincinnati, OH, US
Morris; Suzanne C., Mason, OH, US

IN Finkelman Fred D; Morris Suzanne C

PAF University of Cincinnati, Cincinnati, OH, US

PA Cincinnati, University of (17560)

EXNAM Chin, Christopher L
EXNAM Gabel, Gailene R
AG Frost Brown Todd LLC
PI US 6824986 B1 20041130
AI US 1998-167088 19981006
XPD 6 Oct 2018
PRAI US 1997-61167P 19971006 (Provisional)
FI US 6824986 20041130
DT Utility; Granted Patent - Utility, no Pre-Grant Publication
FS CHEMICAL
GRANTED
OS CA 142:30001
GOVI This invention was made in part with Government support under Grant Nos. R01AI35987 and R01A137180 awarded by the National Institutes of Health. The Government may have certain rights in this invention.
PARN This application is based on U.S. Provisional Patent Application Ser. No. 60/061,167, Finkelman and Morris, filed Oct. 6, 1997.
MRN 009508 MFN: 0021
CLMN 30
OF 7 IFIPAT COPYRIGHT 2006 IFI on STN
AB The present invention involves techniques for evaluating in vivo cytokine production through the in vivo capture of secreting cytokines by labeled cytokine-binding reagents, followed by in vitro measurement of serum levels of captured cytokine. The methods of the present invention make use of the ability of a neutralizing antibody to a cytokine, when injected into a person or expierimental animal, to bind that cytokine and prevent its catabolism, excretion, or binding to a cytokine receptor. This causes the cytokine, which may normally have a very short in vivo half life, to accumulate in vivo as a cytokine/anti-cytokine antibody complex. If the anti-cytokine antibody is either labeled with a molecule that can be bound by another molecule (e.g.; biotin, which is bound by avidin or streptavidin), or is itself capable of being bound by another molecule (e.g.; a rat anti-cytokine antibody could be bound by an anti-rat immunoglobulin antibody), and the cytokine can also be bound by an antibody that recognizes a site distinct on the cytokine molecule from the site bound by the injected, neutralizing antibody, than the concentration of the cytokine/ anti-cytokine complex in serum or other biological fluid can easily be assayed by a modified ELISA. This assay may be used with target analytes other than cytokines, which may include hormones, drugs or other analytes in a human or aninial. The target analyte is preferably a macromolecule, more preferably a protein, and most preferably a cytokine.

L10 ANSWER 4 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
AN 2004-831010 [82] WPIDS <<LOGINID::20060522>>
DNN N2004-656433 DNC C2004-288785
TI Measuring production of secreted cytokines in human or animal by injecting human or animal with labeled ***targeting*** ***moiety*** , allowing moiety to circulate through human or animal, and detecting amount of complexes in obtained sample.
DC B04 D16 S03
IN FINKELMAN, F D; MORRIS, S C
PA (UYCI-N) UNIV CINCINNATI
CYC 1
PI US 6824986 B1 20041130 (200482)* 11
ADT US 6824986 B1 Provisional US 1997-61167P 19971006, US 1998-167088 19981006
PRAI US 1997-61167P 19971006; US 1998-167088 19981006

AB US 6824986 B UPAB: 20041223
NOVELTY - Measuring production of secreted target analyte of interest in human or animal by injecting human or animal with labeled neutralizing ***targeting*** ***moiety*** , allowing moiety to circulate through human or animal for defined period of time, obtaining sample from human or animal, combining sample with capture moiety, incubating assay mixture to allow capture moiety to bind to conjugate and form complexes in mixture, detecting amount of complexes.
DETAILED DESCRIPTION - Measuring (M1) the production of a secreted target analyte of interest in a human or animal, involves injecting the human or animal with an amount of labeled neutralizing ***targeting*** ***moiety*** , where the ***targeting*** ***moiety*** binds specifically to the target analyte, and the ***targeting*** ***moiety*** is injected in sufficient quantity that a measurable fraction of target analyte is bound by the labeled neutralizing ***targeting*** ***moiety*** , allowing the ***targeting*** ***moiety*** to circulate through the injected human or animal for a defined period of time sufficient to bind to the target analyte of interest and form a ***targeting*** ***moiety*** :target analyte conjugate, where the formation of the ***targeting*** ***moiety*** :target analyte conjugate decreases the clearing rate of the target analyte, obtaining a sample of blood from the human or animal after the defined period of time, combining the sample of blood with a capture moiety where the capture moiety binds specifically to the ***targeting*** ***moiety*** :target analyte conjugate in order to form an assay mixture, incubating the assay mixture to allow the capture moiety to bind to the ***targeting*** ***moiety*** :target analyte conjugate and form ***targeting*** ***moiety*** :target analyte:capture moiety complexes in the assay mixture, removing any unbound and unconjugated ***targeting*** ***moiety*** and target analyte from the assay mixture, detecting the amount of labeled ***targeting*** ***moiety*** :target analyte:capture moiety complexes, where the amount of labeled ***targeting*** ***moiety*** :target analyte:capture moiety complexes detected provides a measure of the production of secreted target analyte in the sample during the defined period of time, and where the secreted target analyte is a secreted cytokine, secreted peptide or secreted protein hormone.
USE - (M1) is useful for measuring the production of a secreted target analyte of interest (preferably cytokines) in a human or animal (claimed). (M1) is useful for detecting a monitoring immunological function in a human or animal.
ADVANTAGE - (M1) enables accurate measurement of the production of cytokines in vivo.
Dwg.0/0

L10 ANSWER 5 OF 7 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
AN 2004-180269 [17] WPIDS <<LOGINID::20060522>>
DNC C2004-071231
TI Composition useful for inhibiting growth of cancer cells in mammalian subject, comprising ***urease*** enzyme in a carrier.
DC A96 B04 D16
IN CHAO, H; DICKSTEIN, J; DOCHERTY, J; MCELROY, J; SEGAL, D; WONG, W; WONG, W Y
PA (CHAO-I) CHAO H; (DICK-I) DICKSTEIN J; (DOCH-I) DOCHERTY J; (MCEL-I) MCELROY J; (SEGA-I) SEGAL D; (WONG-I) WONG W; (HELI-N) HELIX BIOPHARMA CORP
CYC 106

PI WO 2004009112 A1 20040129 (200417)* EN 100
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
US 2004115186 A1 20040617 (200440)
AU 2003250658 A1 20040209 (200450)
BR 2003012664 A 20050503 (200531)
EP 1530482 A1 20050518 (200533) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
NO 2005000793 A 20050418 (200535)
US 2005196391 A1 20050908 (200559)
JP 2006501196 W 20060112 (200604) 67
CN 1681528 A 20051012 (200612)
MX 2005000778 A1 20050901 (200617)

ADT WO 2004009112 A1 WO 2003-CA1061 20030716; US 2004115186 A1 Provisional US 2002-397244P 20020718, US 2003-621833 20030716; AU 2003250658 A1 AU 2003-250658 20030716; BR 2003012664 A BR 2003-12664 20030716, WO 2003-CA1061 20030716; EP 1530482 A1 EP 2003-764850 20030716, WO 2003-CA1061 20030716; NO 2005000793 A WO 2003-CA1061 20030716, NO 2005-793 20050215; US 2005196391 A1 Provisional US 2002-397244P 20020718, CIP of US 2003-621833 20030716, US 2005-46271 20050127; JP 2006501196 W WO 2003-CA1061 20030716, JP 2004-522053 20030716; CN 1681528 A CN 2003-822307 20030716; MX 2005000778 A1 WO 2003-CA1061 20030716, MX 2005-778 20050118

FDT AU 2003250658 A1 Based on WO 2004009112; BR 2003012664 A Based on WO 2004009112; EP 1530482 A1 Based on WO 2004009112; JP 2006501196 W Based on WO 2004009112; MX 2005000778 A1 Based on WO 2004009112

PRAI US 2002-397244P 20020718; US 2003-621833 20030716; US 2005-46271 20050127

AB WO2004009112 A UPAB: 20040310

NOVELTY - A composition (I) comprising an ***urease*** enzyme in a carrier for use in inhibiting growth of cancer cells in a mammalian subject.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) use of ***urease*** enzyme in the manufacture of a medicament for treating or diagnosing cancer in a mammalian subject; and

(2) a gene therapy composition (II) for use in inhibiting growth of cancer cells in a mammalian subject, comprising a targeting vector effective, when administered to the subject, of selectively transfecting cancer cells, and carried in the vector, a recombinant nucleic acid sequence effective to produce a ***urease*** mRNA in transfected cancer cells.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Inhibitor of growth of cancer cells; Gene therapy (claimed).

Athymic nu/nu female mice with human mammary gland adenocarcinoma xenografts were used for testing. Animals selected were generally 5-7 weeks of age, and their body weights at treatment commencement ranged from approximately 15-28 grams. MCF-cells (0.8 multiply 106) were used to generate the xenografts. The cells were grown in modified eagle medium (MEM) media supplemented with Penicillin/Streptomycin 5000 U/ml, L-glutamine 200 mM, sodium pyruvate, non-essential amino acids, vitamins, and 10% fetal bovine serum (FBS). The cell incubator was maintained with 5% CO2, 37.50 deg. C, and 80% humidity. The cells were harvested with 0.25% trypsin-0.03% EDTA solution. Approximately 1 multiply 106 cells in 100 micro l was injected subcutaneously to the right flank of each mouse. Tumor growth was allowed to proceed for about 6-8 days allowing the size of the tumor to reach at least 2-4 mm in diameter. Doses of ***urease*** enzymes were administered by intratumor injection. The dose volume for each animal was 50 micro l. Each solid tumor was injected with the given dose of test article in a fanning fashion. Tumor volumes were taken by external caliper measurements. Body weights were taken at the start of the trial and at time of sacrifice. Results, showed that tumors were not perceptible 24 hours following treatment.

USE - (I) is useful for inhibiting growth of cancer cells such as solid tumor. ***Urease*** enzyme is useful manufacture of a medicament for treating or diagnosing cancer in a mammalian subject. The medicament is useful for treating a solid tumor in a mammalian subject, for treating a solid tumor in a subject who is being treated with a weakly basic anti-tumor compound whose effectiveness is reduced by a higher intracellular/lower extracellular pH gradient in a solid tumor, and for generating diagnostic information about the pH within a solid tumor region in a subject. (II) is useful for inhibiting growth of cancer cells in a mammalian subject (claimed).

Dwg.0/5

L10 ANSWER 6 OF 7 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
AN 2004-09515 BIOTECHDS <<LOGINID::20060522>>
TI Composition useful for inhibiting growth of cancer cells in mammalian subject, comprising ***urease*** enzyme in a carrier; enzyme composition and antibody for use in disease therapy and gene therapy
AU CHAO H; WONG W; SEGAL D; MCELROY J; DOCHERTY J; DICKSTEIN J
PA HELIX BIOPHARMA CORP
PI WO 2004009112 29 Jan 2004
AI WO 2003-CA1061 16 Jul 2003
PRAI US 2002-397244 18 Jul 2002; US 2002-397244 18 Jul 2002
DT Patent
LA English
OS WPI: 2004-180269 [17]
AB DERWENT ABSTRACT:

NOVELTY - A composition (I) comprising an ***urease*** enzyme in a carrier for use in inhibiting growth of cancer cells in a mammalian subject.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) use of ***urease*** enzyme in the manufacture of a medicament for treating or diagnosing cancer in a mammalian subject; and (2) a gene therapy composition (II) for use in inhibiting growth of cancer cells in a mammalian subject, comprising a targeting vector effective, when administered to the subject, of selectively transfecting cancer cells, and carried in the vector, a recombinant nucleic acid sequence effective to produce a ***urease*** mRNA in transfected cancer cells.

WIDER DISCLOSURE - A kit for use in inhibiting growth of cancer cells in a mammalian subject, is also disclosed.

BIOTECHNOLOGY - Preferred Composition: (I) includes a chemical entity effective to enhance the delivery of the enzyme to cancer cells, when the composition is administered to the subject. The chemical entity includes a hydrophilic polymer, conjugated to ***urease*** , and is chosen from polyethylene glycol, polyvinylpyrrolidone, polyvinylmethylether, polyhydroxypropyl methacrylamide, polyhydroxypropyl

methacrylate, polyhydroxyethyl acrylate, polymethacrylamide, polydimethylacrylamide, polymethyloxazoline, polyethyloxazoline, polyhydroxyethyloxazoline, polyhydroxypropyoxazoline, polyaspartamide, and hydrophilic cellulose derivatives, where the chemical entity is present in an amount to extend the blood circulation time or reduce the antigenicity of the composition relative to native ***urease*** . The hydrophilic polymer is polyethylene glycol having a molecular weight between 1000 and 10000 daltons. The chemical entity is a ***targeting*** ***moiety*** attached to the ***urease*** and chosen from an anti-tumor antigen antibody, anti-hCG antibody, and a ligand capable of binding specifically to cancer-cell surface receptors. The ***targeting*** ***moiety*** is a polypeptide, and (I) is a fusion protein of the ***targeting*** ***moiety*** and ***urease*** enzyme. The ***urease*** includes, at its C- or N-terminus, a first coil-forming peptide with a selected charge and an ability to interact with a second, oppositely charged coil-forming peptide to form a stable alpha-helical coiled-coil heterodimer, and the chemical entity includes a ***targeting*** ***moiety*** which includes the second coil-forming peptide. The chemical entity includes vesicles having ***urease*** enzyme in entrapped form. The vesicles are liposomes which are long-circulating by virtue of an exterior coating of polyethylene glycol chains, and sized to extravasate into tumor regions, when (I) is administered intravenously. The vesicles are liposomes having surface bound targeting moieties chosen from an anti-tumor antigen antibody, anti-hCG antibody, and ligands capable of binding specifically to cancer-cell surface receptors. The chemical entity includes a ***urease*** inhibitor associated with it, in an amount sufficient to inhibit the activity of the enzyme. The ***urease*** is a plant or bacterial ***urease*** . (I) further comprises an agent chosen from urea, an active anti-tumor agent and an imaging agent. (I) further includes vesicles containing the ***urease*** and agent in entrapped form. (I) further comprises a weakly basic anti-tumor compound whose effectiveness is reduced by a higher intracellular/lower extracellular pH gradient in a solid tumor. The anti-tumor compound is chosen from doxorubicin, daunorubicin, mitoxanthrone, epirubicin, mitomycin, bleomycin, vinca alkaloids such as vinblastine and vincristine, alkylating agents such as cyclophosphamide and mechlorethamine hydrochloride, and antrineoplastic purine and pyrimidine derivatives. In (II), the vector is an adenovirus. The sequence encodes ***urease*** and a secretory leader sequence effective to promoter secretion of the ***urease*** from the transfected cancer cells.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Inhibitor of growth of cancer cells; Gene therapy (claimed). Athymic nu/nu female mice with human mammary gland adenocarcinoma xenografts were used for testing. Animals selected were generally 5-7 weeks of age, and their body weights at treatment commencement ranged from approximately 15-28 grams. MCF-cells (0.8x106) were used to generate the xenografts. The cells were grown in modified eagle medium (MEM) media supplemented with Penicillin/Streptomycin 5000 U/ml, L-glutamine 200 mM, sodium pyruvate, non-essential amino acids, vitamins, and 10% fetal bovine serum (FBS). The cell incubator was maintained with 5% CO2, 37.50 degrees Centigrade, and 80% humidity. The cells were harvested with 0.25% trypsin-0.03% EDTA solution. Approximately 1x106 cells in 100 microl was injected subcutaneously to the right flank of each mouse. Tumor growth was allowed to proceed for about 6-8 days allowing the size of the tumor to reach at least 2-4 mm in diameter. Doses of ***urease*** enzymes were administered by intratumor injection. The dose volume for each animal was 50 microl. Each solid tumor was injected with the given dose of test article in a fanning fashion. Tumor volumes were taken by external caliper measurements. Body weights were taken at the start of the trial and at time of sacrifice. Results, showed that tumors were not perceptible 24 hours following treatment.

USE - (I) is useful for inhibiting growth of cancer cells such as solid tumor. ***Urease*** enzyme is useful manufacture of a medicament for treating or diagnosing cancer in a mammalian subject. The medicament is useful for treating a solid tumor in a mammalian subject, for treating a solid tumor in a subject who is being treated with a weakly basic anti-tumor compound whose effectiveness is reduced by a higher intracellular/lower extracellular pH gradient in a solid tumor, and for generating diagnostic information about the pH within a solid tumor region in a subject. (II) is useful for inhibiting growth of cancer cells in a mammalian subject (claimed).

ADMINISTRATION - (I) is administered by parenteral, enteral, transepithelial, transmucosal, transdermal, and/or surgical in dosages ranging from 0.1-1000 international units. (100 pages)

L10 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:985203 CAPLUS <<LOGINID::20060522>>
DN 143:260354
TI Method and composition using a weakly basic anticancer compound and ***urease*** for inhibiting cancer cell growth
IN Segal, Donald; McElroy, Jerry; Chao, Heman; Wong, Wah Y.; Docherty, John; Dickstein, Jodi
PA Helix Biopharma Corporation, Can.
SO U.S. Pat. Appl. Publ., 30 pp., Cont.-in-part of U.S. Ser. No. 621,833.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 2005196391 | A1 | 20050908 | US 2005-46271 | 20050127 |
| | US 2004115186 | A1 | 20040617 | US 2003-621833 | 20030716 |
| PRAI | US 2002-397244P | P | 20020718 | | |
| | US 2003-621833 | A2 | 20030716 | | |

AB Improvements in methods of treating cancer with weakly basic anticancer compds. are provided. In one aspect, the invention provides an improvement in a method of treating cancer cells whose extracellular environment contains 1-8 mM urea, by exposing the cells to a weakly basic anticancer compd. which is effective in inhibiting the growth of the cells. The improvement includes (a) exposing the cells to a ***urease*** enzyme compn. and, (b) by step (a), reducing the amt. of anticancer compd. required to produce a given extent of inhibition in the growth of the cells when the cells are exposed to the anticancer agent. Methods of potentiating the specific therapeutic activity of a weakly basic anticancer compd. in the treatment of a given mammalian cancer which is responsive to the compd. are provided as are pharmaceutical compns. for use in i.v. administration to a subject are also provided.

=> index biosci -uspatfull -uspat2 -dgene
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    41.81     103.31

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                    -0.75      -2.25

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      AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
      CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DISSABS, DRUGB,
      DRUGMONOG2, DRUGU, EMBAL, EMBASE, ESBIOBASE, ...'
ENTERED AT 12:47:08 ON 22 MAY 2006

65 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

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               1   FILE EMBASE
               1   FILE JICST-EPLUS
               5   FILE MEDLINE
               1   FILE PASCAL
               1   FILE SCISEARCH
               2   FILE TOXCENTER
               1   FILE VETU
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               2   FILE TOXCENTER
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L6             8 S L5 AND TARGET?

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                SEA (TARGETING (W) MOIETY) AND UREASE
                ---------
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                1   FILE BIOTECHDS
                1   FILE CAPLUS
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L8              QUE (TARGETING (W) MOIETY) AND UREASE
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L10            7 S L8
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     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ESBIOBASE, ...' ENTERED AT 12:47:08 ON
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                0*  FILE ANTE
                SEA UREASE (P) CANCER (P) TREAT?
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                1   FILE ANABSTR
                0*  FILE ANTE
                0*  FILE AQUALINE
                1*  FILE BIOENG
               38   FILE BIOSIS
                0*  FILE BIOTECHABS

=> log h
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               9.15     112.46

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                 ENTRY    SESSION
CA SUBSCRIBER PRICE                               0.00      -2.25

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:55:58 ON 22 MAY 2006
```